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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

St. Louis, Missouri
April 5, 2000

CERTIFICATE OF MAILING

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In re application of: Wold	:	
Serial No.: 09/111,911	:	Examiner Gai (Jennifer) Lee
Filed: July 8, 1998	:	Group Art Unit 1632
For: INHIBITING APOPTOSIS WITH ADENOVIRUS RID PROTEIN	:	

Assistant Commissioner for Patents
Washington, D.C. 20231

DECLARATION OF DR. WILLIAM S. M. WOLD UNDER 37 C.F.R. §1.132

I, William S. M. Wold, declare as follows:

I reside at 1609 Adgers Wharf, Chesterfield, Missouri 63017.

I received my Bachelor of Science degree in 1965 and my Master of Science degree in 1968, from the University of Manitoba, at Winnipeg, Canada. I was awarded a Ph.D. in 1973, also from the University of Manitoba. I have held a number of different faculty and research positions since 1973 and in recent years I have been the Associate Director of the Specialized Cancer Center, Institute of Molecular Virology, St. Louis University School of Medicine, St. Louis, MO (1977 - 1980); Associate Professor (1979 - 1986) and Professor (1986 - 1992) of the Institute of Molecular Virology, St. Louis University School of Medicine; Professor and Chairman of the Department of Molecular Microbiology and Immunology, St. Louis University School of Medicine (1992 - Present); and Member of the Pediatric

Research Institute, St. Louis University School of Medicine (1995 - Present). I served as the President and Chief Executive Office of VirRx, L.L.C. during 1999.

I was selected as the Cancer Research Campaign Lecturer for the British Biochemical Society, 42nd Harden Conference, Wye College, Kent, UK (1994), and have received the NIH Research Career Development Award (1980 - 1985), as well as several pre- and postdoctoral fellowships.

During my term as a faculty member at St. Louis University School of Medicine, I have been responsible for the training of six doctoral students and twenty four post-doctoral fellows, as well as teaching in a number of areas in the fields of microbiology, molecular genetics and virology.

During the past ten years, I have served on a number of University-wide committees and panels at St. Louis University that have dealt with strategic planning and administration of health sciences research and education. I presently serve as an extramural advisor for the Canadian National Cancer Institute. I have participated in eleven grant reviews on behalf of the NIH during the past ten years.

I have served on the editorial board of the *Journal of Virology* (1997 - 1999), and presently serve on the editorial boards of the journals *Virology* (1989 - Present), *J. Virol.* (1998 - Present), and *Virol. Immunology* (1999 - Present). I have also provided *ad hoc* review for seventeen other authoritative journals in the field of science and medicine including *Cancer. Res., Gene, Genome Research, J. Biol. Chem., J. Immunol., J. Infect. Dis., J. Natl. Cancer Inst., Molec. Cell. Biol., Nature, Oncogene, Proc. Natl. Acad. Sci. USA, Science, Trends Microbiol.*, and *Virus Res.* I am a member of the American Society for Microbiology, the American Society for Virology, and the American Society for the Advancement of Science.

My research interests are in the fields of genetic and biochemical analysis of a variety of adenovirus proteins that function in human adenovirus pathogenesis and other activation and regulatory roles; the function of the E3-14.7K protein, the E3 RID complex of membrane proteins, and the E1B-19K protein in preventing apoptosis and inflammation induced by death ligands in the tumor necrosis factor family; functions of E3 RID in stimulating endosome/lysosome-mediated internalization and degradation of cell-surface Fas, TRIAL, and the epidermal growth factor receptor; function of the novel Adenovirus Death Protein; and characterization of the adenovirus subgroup C E3-6.7K endoplasmic reticulum membrane protein. I am also interested in the use of adenovirus as a vector for somatic cell gene therapy and for cancer therapy. This work is presently supported by grants, which, over their lives, have provided over two million dollars of direct cost support.

I have authored, or have in preparation, 153 journal articles. I have been an invited plenary session lecturer at 23 symposia, and have been an invited lecturer on 59 other occasions. My resume, a copy of which is attached, provides the details of these publications and presentations.

I am the sole inventor of the subject matter covered in U.S. Patent Application Serial No. 09/111,911 (the application that is presently at issue), and have studied the specification and claims of that application as well as the Office Action dated December 6, 1999.

Based upon my experience and understanding of the technology involved, it is my scientific opinion that the specification of the present application, when read in light of the general state of knowledge in the art of molecular biology on July 8, 1998, the date on which this application was filed, would enable one of ordinary skill in the relevant art to practice the full scope of the invention that is claimed in this application. My reasons for this opinion follow.

The rationale behind the invention is stated throughout the application, and can be summarized as follows. The immune system responds to "foreign" proteins, such as those present on viruses, bacteria, and tumor cells, by attempting to kill cells (target cells) that are expressing these proteins. In the early innate part of the immune response, killing is mediated by macrophages and natural killer (NK) cells. In the later immune-specific stage, antigen-specific cytotoxic T-lymphocytes (CTL) are formed, and these also attack and kill target cells. CTL and NK killing is mediated in large part through the "perforin-granzyme" pathway. However, with CTL (and also perhaps NK cells and macrophages), killing is also mediated by death ligands expressed on the CTL, namely Fas ligand (FasL), tumor necrosis factor (TNF), and TNF related apoptosis inducing protein (TRAIL). These ligands engage their cognate receptors on target cells and activate a Programmed Cell Death (apoptosis) pathway.

The receptors for FasL, TNF, and TRAIL are expressed on most cell types in the body, consistent with the general role that they play in eliminating infected or cancerous cells. In addition, the Fas-FasL system plays a very important role in maintaining normal physiological levels of T-lymphocytes including CTL (Nagata, *Cell* 88:355-365,1997). As stated by Nagata (*Cell* 88:355-365, 1997), "Fas is ubiquitously expressed in various tissues with abundant expression in the thymus, heart, and kidney." "FasL is predominantly expressed in activated T lymphocytes and natural killer cells." During an infection, CTL become activated and proliferate to high levels. When the infection is cleared, the excess CTL must be destroyed. This is accomplished by FasL and Fas expressed on the CTL becoming engaged and inducing apoptosis in the CTL.

Adenoviruses have evolved mechanisms to inhibit apoptosis induced by killer cells of the immune system. One such mechanism is the adenovirus E3 protein named RID. RID consists of two subunits, named RIDα and RIDβ. RID inhibits apoptosis mediated through the Fas, TNF, and TRAIL pathways (Wold et. al., *Curr. Opin. Immunol.* 11:380-386, 1999; Mahr and Gooding, *Immunological Reviews* 168:121-130, 1999). RID is expressed within cells, and it functions to cause the receptors Fas, TNF receptor 1 (TNFR1), TRAIL receptor 1 (TRAIL-R1), and TRAIL receptor 2 (TRAIL-R2) to be

internalized from the cell surface and degraded in lysosomes. Inasmuch as these receptors no longer exist to mediate apoptosis, RID inhibits apoptosis through the Fas, TNF, and TRAIL pathways.

The present invention seeks to exploit the properties of RID in treating cancer, in facilitating tissue transplantation, and in treating degenerative and immunodeficiency diseases. Regarding cancer, the invention focuses on the observation that some cancer cell types lack Fas and express FasL (the reverse is true for the vast majority of cells). As a result, the cancer cells kill CTL via FasL on the cancer cell stimulating Fas on the CTL. Accordingly, the cancer cells are resistant to CTL. In the present invention, RID is used to eliminate the Fas on the CTL. As such, the CTL will not be killed by the cancer cell, and will be free to kill the cancer cell by, e.g., the perforin-granzyme system. The present method teaches the removal of leukocytes from cancer patients, the introduction of RID into the cells, then the reinsertion of the cells into the patient. RID will remove Fas from the surface of the CTL, thereby preventing cancer cells from killing the CTL. Thus, the CTL will be able to kill the cancer cells. Adenoviruses are known to infect lymphoid cells and to express adenovirus proteins (Lavery *et. al.*, *J. Virol.* 61:1446-1472, 1987). A skilled artisan would reasonably expect, based on Examples 1-6 and 9, that RID expressed in leukocytes would inhibit Fas-mediated apoptosis in leukocytes.

The success of tissue transplantation in humans is limited by the fact that the recipient's immune system perceives the transplanted tissue to be foreign. Accordingly, CTL, NK cells, and other immune mechanisms attack the transplanted tissue and destroy it. As mentioned, CTL and probably NK cells kill targets when death ligands such as FasL, TNF, and TRAIL that are expressed on the CTL cell surface engage their cognate receptors, Fas, TNFR1, TRAIL-R1, and TRAIL-R2 on the target cells. In this example, the transplanted cells are the target cells. Based on the known functions of RID, a skilled artisan would reasonably expect that RID expressed in transplanted cells would inhibit destruction (apoptosis) of the transplanted cells by the CTL of the transplant recipient.

Degenerative autoimmune diseases that are associated with Fas dysfunction include hypereosinophilic syndrome (Lenardo et. al., *J. Exp. Med.* 183:721-724, 1996), hepatitis (Kondo et. al., *Nat. Med.* 3:409-413, 1997), and Hashimoto's disease (Giordano et. al., *Science* 175:960-963, 1997). These diseases are analogous to the scenario with cancer cells and CTL as discussed above. That is, the diseased tissues inappropriately express FasL, which interacts with Fas on neighboring cells and destroys them. Again, we propose that expression of RID in the cells of these tissues will down-regulate Fas, thereby preventing the destruction of the cells. A skilled artisan would expect that RID expressed in the cells of these tissues would inhibit apoptosis via the Fas pathway.

At the top of page 3 of the Office Action, it was argued that the claims are not enabled because the specification fails to supply critical guidance as to the effective amounts, effective frequencies and stability of delivery of the complex or gene, or vectors containing the RID complex sequence. However, Figure 6 in the application shows that Fas-mediated apoptosis is inhibited when cells are transiently

transfected with two plasmid vectors, one expressing RIDα and the other expressing RIDβ. The effective dose of each plasmid is 2.5 μg, as described in line 20 of page 19 of the application. Figure 11 shows that Fas is cleared from the cell surface into vesicles (many of the vesicles are lysosomes) when cells are transiently transfected with the two plasmids expressing RIDα and RIDβ. Figures 14 and 15 show that Fas is degraded when cells are transiently transfected with the plasmids expressing RIDα and RIDβ. In experiments similar to those in Figures 11, 14, and 15, the effective dose can be as little as 0.5 μg of RIDα plasmid and 0.1 μg of RIDβ plasmid. A skilled artisan would expect that similar amounts of the RIDα and RIDβ plasmids would be sufficient to inhibit Fas-mediated apoptosis.

With respect to the dose of RID required when RID is administered to cells by means of expression in cells from the 231-10 vector, vector doses of 250 plaque forming units per cell (250 PFU/cell) are effective, as described in line 4 of page 29 for down-regulation of TNFR1 (Figure 22A and 22B). In the case of Example 9, when human A549 cells were mock-infected or infected with the 231-10 vector, then injected into the hind flanks of C57/BL6 or Balb/c mice, the dose of infection was 50 PFU/cell of 231-10. This dose was sufficient to allow the A549 cells to grow into a tumor. The PFU/cell used in Example 9 is described in line 3 and lines 14 and 15 of page 31.

With respect to "effective frequencies," one treatment is sufficient, as described in all the figures describing transient transfections of the RIDα- and RIDβ-expressing plasmids, and in the figures describing infections with the 231-10 vector.

With respect to stability of the RID complex when the RIDα and RIDβ proteins are expressed from these vectors, the RID proteins are readily detectable in cells using standard methods such as immunoprecipitation, immunoblot, and immunofluorescence. Detection of one or both of the RID proteins is shown in Figures 6C, 11C, 11E, 11G, 22B, 26, 29, and 30B. Figure 26 shows levels of the adenovirus RIDβ, 14.7K, and gp19K proteins extracted from 2 week old tumors formed by 231-10-infected cells following implantation into C57/BL6 mice. Figure 29 shows these same adenovirus proteins at 1-5 days postinfection of cultured A549 cells (page 33, beginning on line 30). Thus, the RID protein is stable.

At page 3, line 5, the Action has maintained that there was no guidance as to the promoters regulating the expression of the RID sequence. When the RIDα and RIDβ genes are provided by an adenovirus vector such as 231-10, or by plasmid vectors such as described in this application, the genes do not normally integrate into cellular DNA, and integration is not necessary for RID to function. The RID genes must integrate when they are provided using AAV or retrovirus vectors; however, the amounts of these vectors needed for these types of vectors to integrate are well known by a skilled artisan and would not require undue experimentation.

At line 7 of page 3 of the Action, it was argued that the specification did not provide any readily available assays that would permit the determination of the complexes of RID. However, methods for

detection of the RID proteins, and methods to assay RID function, are presented throughout the application, and are familiar to a skilled artisan. Immunoprecipitations, co-immunoprecipitations, immunoblots, and immunofluorescence are standard methods, and are described in detail in the following publications listed in "Other Prior Art": Carlin et. al., *Cell* 57:135-144, 1989; Dimitrov et. al., *J. Virol.* 71:2830-2837, 1997; Krajcsi et. al., *J. Virol.* 70:4904-4913, 1996; Stewart et. al., *J. Virol.* 69:172-181, 1995; Tollefson et. al., *Nature* 392:726-730, 1998; Tollefson et. al., *J. Virol.* 65:3095-3105, 1991. Examples in the application describe experiments wherein the RID proteins are administered to cells by wild-type adenovirus infections, 231-10 infection, or RIDα plus RIDβ plasmid transfection, and wherein assays for RID functions are described. The experiments employ standard methods, *e.g.*, flow cytometry, immunofluorescence, immunoblots, confocal microscopy, plasmid transfections, virus infections, and ^{51}Cr-release (Figures 16A, 16B, 17). The experiments are described in sufficient detail for them to be repeated and extended by a skilled artisan.

On page 4, and continuing at the top of page 5, the Action argues that gene therapy in general was regarded as unpredictable by the art at the time of the filing, and that the unpredictability lay principally in the expression and delivery of the gene. However, it should be realized that the present invention is not directly relevant to the statements made in the cited reviews pertaining to gene therapy (Verma and Somia, 1997; Blau and Springer, 1995; Marshall, 1995; Tio et. al., 1998; Anderson, 1998). The term "gene therapy" refers to the correction of genes that are mutated, and to techniques whereby the correct versions of mutated genes are introduced into whole organisms such as humans. There are indeed difficulties associated with gene therapy, but the field is in its early stages of development and awaits new inventions. In the present invention, what is proposed is to introduce two "foreign" genes into humans, those for the adenovirus RIDα and RIDβ proteins. There is no attempt to correct a genetic defect, rather what is intended is to inhibit an intrinsic cellular process, namely apoptosis.

The *in vitro* and *ex vivo* data provided in the specification fully support the premise that RID inhibits apoptosis induced through the death domain receptors Fas, TNFR1, TRAIL-R1, and TRAIL-R2. It is shown that RID is expressed in cells in effective amounts to inhibit apoptosis.

In the first full paragraph on page 5, a reference by Deigner *et al.* is cited to support an argument that there is similar unpredictability associated with the modulation of apoptosis. But the statement by Deigner et. al., "that the CD95/APO-1/Fas pathway is frequently nonfunctional in human malignancies" is of minimal relevance because of the mechanism by which this occurs (*e.g.* Hahne et al., *Science* 275:960-963, 1996; O'Connell et. al., *Nature Med.* 5:267-268, 1999). As is discussed on the bottom of page 2 and the top of page 3 in the application, in some cancer cells, Fas (a receptor) is down-regulated and FasL (a ligand for Fas) is up-regulated. As a result, the cancer cells are not killed through the Fas pathway by CTL, rather the cancer cells kill the CTL via the FasL expressed on the cancer cell and Fas expressed on the CTL. Indeed, these observations form the basis for present claims 17-22, as described in

lines 13 to 16 on page 5 of the application. There, it is proposed that leukocytes can be withdrawn from a cancer patient, then treated with RID (*e.g.* by infecting the cells with the 231-10 vector which expresses RID), then reintroduced into the patient. RID will remove Fas from the surface of the leukocytes and cause it to be degraded. Because the leukocytes no longer express Fas, they cannot be killed via the Fas pathway by the FasL-expressing cancer cells. Instead, the CTL will be able to kill the cancer cell via the leukocyte's major killing pathway, the perforin-granzyme pathway (Nagata, *Nature Med.* 2:1306-1307, 1996; Nagata, *Cell* 88:355-365, 1997). These same arguments apply to natural killer cells and macrophages.

Towards the middle of page 5 of the Action, the Deigner et al. reference is again cited to support the premise that pharmacological modulation of PCD will remain a challenge to improve the efficacy of established drugs. However, the present application describes a novel method by which Programmed Cell Death (apoptosis) can be inhibited. Inasmuch as RID probably evolved over millions of years in adenoviruses as a means to inhibit apoptosis through death domain receptors, a skilled artisan would reasonably expect that RID will be efficacious in inhibiting apoptosis when administered therapeutically.

Towards the bottom of page 5 of the Action, a reference by Tio et al. is cited to disclose that adenovirus-mediated gene therapy has a major limitation -- it can elicit a cellular immune response to viral or transgene antigens that result in destruction of the transfected cell. Therefore, it is argued, the uncertainties involving the stability of expression and toxicity of Fas at the time of the present invention would not have provided a reasonable expectation of success for apoptosis gene therapy involving RID. However, as discussed on the bottom of page 3 of the application, proteins such as RID, which are encoded by the adenovirus E3 transcription unit, function in adenovirus biology to prevent infected cells from being destroyed by killer cells of the immune system (see Wold et. al., *Current Opin. Immunol.* 11:380-386, 1999; Mahr and Gooding, *Immunological Reviews* 168:121-130, 1999). Most of the adenovirus vectors discussed by Tio et. al. lack the genes for the E3 proteins including RID. Other vectors cited by Tio et. al. retain the E3 genes, but are unable to express them efficiently because the vectors lack the E1A proteins which are required for expression of E3 genes. These vectors have no protection from the immune system. In the case of the present 231-10 vector, expression of RID will inhibit apoptosis of infected cells by killer cells of the immune system. Data in Figures 16A, 16B, 16C, and 17 of the application indicate that RID inhibits apoptosis of cells induced by CTL and NK cells. Data in Figures 24 and 25 establish that E3 proteins expressed by 231-10, including RID, allow human cells to form tumors in immunocompetent mice, very likely because the E3 proteins protect the infected cells from destruction by the mouse's immune system.

The statement towards the bottom of page 5 of the Action pertaining to the toxicity of FasL is not relevant. The present invention does not propose altering the levels of FasL, nor adding agonist antibodies to Fas that trigger the apoptotic function of Fas. In fact, the opposite is proposed: to eliminate the apoptotic function of Fas.

On page 6 of the Action, it is argued that the specification fails to provide guidance for *ex vivo* cell treatment. Although the specification does not provide an example that illustrates each step of decreasing leukocyte apoptosis by withdrawing leukocytes from the patient, treating the leukocytes with an effective amount of a RID complex, and administering the treated leukocytes to the patient, it is my opinion that a skilled artisan would reasonably expect that this protocol will be effective. In other words, a skilled artisan would reasonably expect that leukocytes can be successfully withdrawn from patients, that they can be infected with adenovirus, that RID will undoubtedly degrade Fas, and that lymphocytes can be reintroduced into patients. First, it is well known that leukocytes (and blood) can be removed from patients and then reintroduced into the patient. Second, as is the case with most known cells, including the cells discussed in the application, leukocytes express Fas on their surface (Nagata, *Nature Med.* 2:1306-1307, 1996; Nagata, *Cell* 88:355-365, 1997). Third, the apoptotic pathway mediated through Fas, including the cellular proteins named FADD, Caspase 8, and Caspase 3, is identical or similar in leukocytes and cells such as A549 cells which were used in the examples presented in this application (Nagata, *Annu. Rev. Genet.* 33:29-55, 1999). Fourth, RID clears Fas from the cell surface and inhibits Fas-mediated apoptosis in every cell type tested, including human A549 lung carcinoma cells, human MCF-7 breast carcinoma cells, human HT-29-14S cells, human HeLa cells, human 293 cells, human ME-180 cells, and mouse P815 cells (Tollefson et. al., *Nature* 392:726-730, 1998; Shisler et. al., *J. Virol.* 71:8299-8306, 1997; Elsing and Bugert, *Proc. Natl. Acad. Sci. USA* 95:10072-10077, 1998). Fifth, adenoviruses can productively infect established T-cell lines (Lavery et. al., *J. Virol.* 61:1466-1472, 1987)

At page 6, line 13 of the Action it was stated that there were no indications of controls for Example 9. However, the experiments described in Example 9 were properly controlled. As discussed on page 31 of the application, line 3, in parallel with the 231-10-infected A549 cells, mock-infected A549 cells were also injected into the C57/BL6 mice. As stated on line 7, "with mice that received mock-infected cells, there was a pin-point mass on one flank, and no mass at all on the other flank (data not shown)." (No photograph was taken of these mice because there was little or no tumor to see).

Mock-infected cells were also used in the second experiment, beginning on line 14. The mock-infected cells formed very small masses or no mass at all (lines 21-24). As an additional control, cells were mock-infected or infected with 231-10, frozen and thawed, then injected into C57/BL6 or Balb/c mice; these cells did not form tumors, indicating that the tumors observed with live 231-10-infected cells

required the outgrowth of the A549 cells, not merely infiltration of lymphoid cells into the area where the cells were injected.

At lines 15 and 18 of page 6 of the Action, it should be noted that the mice used in the reported experiments were immunocompetent, not "immunocompromise." As discussed on page 30 of the application, lines 25-31, "cells or tissues transplanted into immunocompetent recipients are usually destroyed (rejected) by immune killer cells of the recipient." Example 9 shows that foreign cells (human A549 cells) can be transplanted into immunocompetent recipients (mice), provided such cells have been infected with the 231-10 vector. The reason that 231-10 allows these cells to be transplanted is that the E3 proteins expressed by 231-10, including RID, prevent the mouse's immune killer cells from destroying the A549 cells. It follows logically that the RID protein will permit other types of tissue transplantation.

At the bottom of page 6 of the Action, the relevance of an example showing the growth of tumors in an "immunocomprimose" [immunocompetent] mouse is questioned relative to the retention of grafts on the basis of apoptosis or the effect on transplant tissue. Arguments as to why the results of Example 9 pertain to decreasing apoptosis in leukocytes, and to why this is a novel and useful invention, have been discussed above.

On page 7, line 10 of the Action, it is questioned whether guidance has been provided as to which cell lines express Fas, TNFR-1, DR3, TRAIL-R1 or TRAIL-R2. But is it well known that "Fas is ubiquitously expressed in various tissues, with abundant expression in the thymus, heart, and kidney" (Nagata, *Cell* 88:355-365, 1997). TNFR1 is ubiquitous. The mRNAs for TRAIL-R1 (also named DR4) and TRAIL-R2 (also named DR5) are widespread, and have been detected in all tissues examined, including thymus, prostate, testes, ovary, small intestine, peripheral blood lymphocytes, heart, and placenta (Pan et. al., *Science* 276:111-113, 1997; Chaudhary et. al., *Immunity* 7:821-830,1997; Walczak et. al., *EMBO J.* 16:5386-5397, 1997). DR3 (also named TRAMP) mRNA has been detected in tissues enriched in lymphocytes, including peripheral blood lymphocytes, thymus, spleen, colon, and small intestine (Chinnaiyan et. al., *Science* 274:990-992, 1996).

At the bottom of page 7 of the Action, it is argued that the specification does not describe a repeatable method for the production of the 231-10 vector. However, the precise method by which 231-10 may be constructed is described in detail such that a skilled artisan would be able to construct it. Figure 27 is a schematic illustration of the vector, and Figure 28 provides the DNA sequence.

At page 9 of the Action, it is maintained that the term "RID" is vague and indefinite. However, the term RID is an acronym for Receptor Internalization and Degradation, as stated on lines 21 and 22 of page 4 of the application. RID is composed of two polypeptide, RIDα and RIDβ, as described in lines 19-21 of page 5, lines 15-27 of page 6, lines 31-35 on page 11, all of page 12, and as shown in Figures 3

and 54. RIDα was previously named E3-10.4K (the predicted molecular weight of the polypeptide is 10,400), RIDβ was named E3-14.5K (predicted molecular weight of 14,500), and RID was named E3-10.4K/14.5K (Tollefson et. al., *J. Virol.* 65:3095-3105, 1991; Tollefson et. al., *Nature* 392:726-730, 1998; Wold et. al., *Curr. Opin. Immunol.* 11:380-386, 1999). RID, RIDα, RIDβ, 10.4K, E3-10.4K, 14.5K, E3-14.5K, 10.4K/14.5K, and E3-10.4K/14.5K have been used interchangeably in the application (e.g., pages 3-6). Using the information presented in the application, and in the bibliography, a skilled artisan will be able to understand the structure of RID and to isolate and use the RIDα and RIDβ genes.

The undersigned declares that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

April 6, 2000
Date:

William S. M. Wold